(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 June 2006 (29.06.2006)

PCT

(10) International Publication Number
WO 2006/068593 A1

(51) International Patent Classification:
C07D 277/62 (2006.01) *C07D 277/64* (2006.01)
A61K 31/381 (2006.01) *C07D 277/68* (2006.01)
A61P 25/00 (2006.01) *C07D 277/82* (2006.01)

(21) International Application Number:
PCT/SE2005/001965

(22) International Filing Date:
19 December 2005 (19.12.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0403118-3 21 December 2004 (21.12.2004) SE

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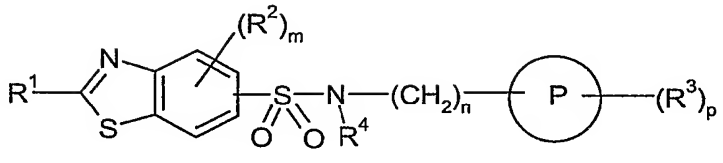
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW BENZOTHIAZOLESULFONAMIDES



(I)

(57) Abstract: The present invention relates to new compounds of formula I, (I) wherein R^1 to R^4 are as defined as in formula I, or salts, solvates or solvated salts thereof, processes for their preparation and to new intermediates used in the preparation thereof, pharmaceutical formulations containing said compounds and to the use of said compounds in therapy.

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NEW BENZOTHIAZOLESULFONAMIDES

FIELD OF THE INVENTION

The present invention relates to new compounds, to pharmaceutical compositions containing said compounds and to the use of said compounds in therapy. The present invention further relates to processes for the preparation of said compounds and to new intermediates used in the preparation thereof.

BACKGROUND OF THE INVENTION

Pain sensation in mammals is due to the activation of the peripheral terminals of a specialized population of sensory neurons known as nociceptors. Capsaicin, the active ingredient in hot peppers, produces sustained activation of nociceptors and also produces a dose-dependent pain sensation in humans. Cloning of the vanilloid receptor 1 (VR1 or TRPV1) demonstrated that VR1 is the molecular target for capsaicin and its analogues. (Caterina,M.J., et al., et.al. Nature (1997) v.389 p 816-824). Functional studies using VR1 indicate that it is also activated by noxious heat , tissue acidification) and other inflammatory mediators (Tominaga,M., et.al. Neuron (1998) v.21, p.531-543). Expression of VR1 is also regulated after peripheral nerve damage of the type that leads to neuropathic pain. These properties of VR1 make it a highly relevant target for pain and for diseases involving inflammation. While agonists of the VR1 receptor can act as analgesics through nociceptor destruction, the use of agonists, such as capsaicin and its analogues, is limited due to their pungency, neurotoxicity and induction of hypothermia. Instead, agents that block the activity of VR1 should prove more useful. Antagonists would maintain the analgesic properties, but avoid pungency and neurotoxicity side effects.
Compounds with VR1 inhibitor activity are believed to be of potential use for the treatment and/or prophylaxis of disorders such as pain, especially that of inflammatory or traumatic origin such as arthritis, ischaemia, fibromyalgia, low back pain and post-operative pain

(Walker et al., J Pharmacol Exp Ther. (2003) Jan; 304(1):56-62). In addition to this visceral pains such as chronic pelvic pain, cystitis, irritable bowel syndrome (IBS), pancreatitis and the like, as well as neuropathic pain such as sciatia, diabetic neuropathy, HIV neuropathy, multiple sclerosis, and the like (Walker et al *ibid*, J Pharmacol Exp Ther. (2003) Mar;304(3):940-8), are potential pain states that could be treated with VR1 inhibiton. These compounds are also believed to be potentially useful for inflammatory disorders like asthma, cough, inflammatory bowel disease (IBD) (Hwang, et al., Curr Opin Pharmacol (2002) Jun;2(3):235-42). Compounds with VR1 blocker activity are also useful for itch and skin diseases like psoriasis and for gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder (Yiangou et al BJU Int (2001) Jun;87(9):774-9, Szallasi, Am J Clin Pathol (2002) 118: 110-21). VR1 inhibitors are also of potential use for the treatment and/or prophylaxis of the effects of exposure to VR1 activators like capsaicin or tear gas, acids or heat (Szallasi *ibid*).

The role for VR1 antagonists in Inflammatory Bowel Diseases (IBD) is further supported by the finding that primary sensory neuron denervation by subcutaneous administration of capsaicin to neonatal rats, resulted in decreased levels of disease activity index (DAI), MPO and histological damage to the gut in DSS colitis model compared to control (N Kihara, et al., Gut, 2003. 52: p. 713-719). TRPV1 antagonists attenuate macroscopic symptoms in DSS colitis model in mice (E. S. KIMBALL, et al., Neurogastroenterol Motil, 2004. 16: p. 1-8).

The potential for a role for VR1 antagonists in Irritable Bowel Syndrome (IBS) has been described. Patients with faecal urgency and rectal hypersensitivity have increased levels of TRPV1 expression in nerve fibres in muscle, submucosal and mucosal layers. This also correlates with increase sensitivity to heat and distension (C L H Chan, et al., THE LANCET, 2003. 361(Feb 1): p. 385-91). Jejunal wide dynamic range (WDR) afferents show lower firing in response to pressure ex vivo in TRPV1-/- mice (Rong W, H.K., et al., J Physiol (Lond). 2004. 560: p. 867-881). The visceromotor responses to jejunal and colorectal distension in rat are affected by a TRPV1 antagonist using both ramp and phasic distensions (Winchester, EMG response to jejunal and colorectal distension in rat are affected by a TRPV1 antagonist in both ramp and phasic distensions. DDW abstract,

2004). Capsaicin applied to the ileum induce pain and mechanical hyperalgesia in human experimental model (Asbjørn Mohr Drewes, et al., Pain, 2003. 104: p. 333-341).

A role in Gastroesophageal Reflux Disease (GERD) for VR1 antagonists has been mentioned in the literature. Patients with oesophagitis have increased levels of TRPV1 expression in peripheral nerves enervating the oesophageal epithelium (P. J. Matthews, et al., European J. of Gastroenterology & Hepatology, 2004. 16: p. 897-902). Even if the TRPV1 antagonist JYL1421 only has minor effects of acid-induced excitation of esophageal afferents, an antagonist with a different profile has yet to be evaluated. Since TRPV1 appears to play a role in mechanosensation, it is possible that antagonists may inhibit TLESRs, the main cause of gastroesophageal reflux.

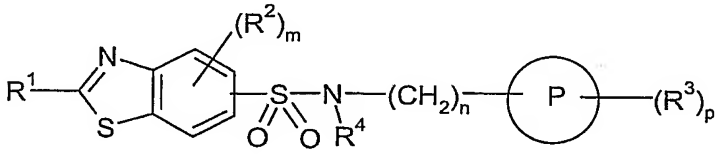
A further portential use relates to the treatment of tolerance to VR1 activators.

VR1 inhibitors may also be useful in the treatment of interstitial cystitis and pain related to interstitial cystitis.

DETAILED DESCRIPTION OF THE INVENTION

The object of the present invention is to provide compounds exhibiting an inhibitory activity at the vanilloid receptor 1 (VR1).

The present invention provides a compound of formula I



(I)

wherein:

ring P is C_{6-10}aryl, C_{3-11}cycloalkyl or C_{5-10}heteroaryl;

R^1 is H, C_{1-4}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, $COOC_{0-6}$alkyl, NH_2, NHC_{1-6}alkyl, $N(C_{1-6}alkyl)_2$, NH(aryl) or $N(aryl)_2$;

R^2 is H, C_{1-4}alkyl, halo, hydroxyC_{0-6}alkyl or C_{1-6}alkylOC_{0-6}alkyl;

m is 0, 1, 2 or 3;

n is 0, 1, 2, 3, 4 or 5;

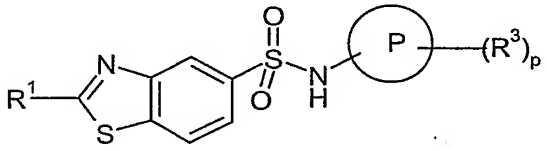
R^3 is NO_2, NH_2C_{0-6}alkyl, halo, $N(C_{1-6}alkyl)_2C_{0-6}$alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{5-6}arylC_{0-6}alkyl, C_{5-6}heteroarylC_{0-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{3-7}heterocycloalkylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, C_{1-6}alkylSC_{0-6}alkyl, C_{1-6}alkylNC_{0-6}alkyl, $(C_{0-6}alkyl)_2NC(O)C_{0-6}$alkyl, $(C_{0-6}alkyl)_2OC(O)C_{0-6}$alkyl or $(C_{0-6}alkyl)_2C(O)OC_{0-6}$alkyl;

p is 1, 2, 3, 4 or 5; and

R^4 is H, C_{1-6}alkyl, arylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl or $N(C_{1-6}alkyl)_2C_{0-6}$alkyl,

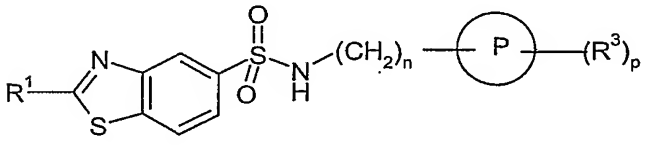
or salts, solvates or solvated salts thereof.

One embodiment of the invention relates to the compound of formula Ib, wherein R^1, R^3, m, p and P are as described above and n is 0 and R^2 and R^4 are H.



(Ib)

Another embodiment of the invention relates to the compound of formula Ic wherein R^1, R^3, m, p and P are as described above and n is 1, 2, 3, 4 or 5 and R^2 and R^4 are H.



(Ic)

In a further embodiment of the invention P is phenyl.

In yet another embodiment of the invention R^1 is methyl or hydroxyC_{1-3}alkyl. In one embodiment R^1 is methyl, hydroxymethyl, hydroxyethyl or hydroxypropyl.

In another embodiment n is 0, 1 or 2.

In yet a further embodiment R^3 is halo, C_{1-3}alkyl, C_{1-3}haloalkyl, C_{5-6}aryl, C_{1-2}alkylO or $(C_{0-6}alkyl)_2NC(O)C_{0-6}$alkyl.

In another embodiment R^3 is phenyl, fluoromethyl, difluoromethyl or trifluoromethyl.

One embodiment of the invention relates to compounds selected from the group consisting of

2-(hydroxymethyl)-*N*-[4-(trifluoromethyl)phenyl]-1,3-benzothiazole-5-sulfonamide,

N-biphenyl-4-yl-2-(hydroxymethyl)-1,3-benzothiazole-5-sulfonamide,

2-(hydroxymethyl)-*N*-[3-(trifluoromethyl)phenyl]-1,3-benzothiazole-5-sulfonamide,

2-(hydroxymethyl)-*N*-[4-(trifluoromethyl)benzyl]-1,3-benzothiazole-5-sulfonamide,

2-(hydroxymethyl)-*N*-[3-(trifluoromethyl)benzyl]-1,3-benzothiazole-5-sulfonamide,

N-(4-isopropoxyphenyl)-2-methyl-1,3-benzothiazole-5-sulfonamide,

N-(4-tert-butylphenyl)-2-methyl-1,3-benzothiazole-5-sulfonamide,

2-methyl-N-[6-(trifluoromethyl)pyridin-3-yl]-1,3-benzothiazole-5-sulfonamide,

2-methyl-N-[3-(trifluoromethyl)phenyl]-1,3-benzothiazole-5-sulfonamide,

N-(4-bromophenyl)-2-methyl-1,3-benzothiazole-5-sulfonamide,

2-methyl-N-[2-(4-methylphenyl)ethyl]-1,3-benzothiazole-5-sulfonamide,

N-[2-(4-bromophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-sulfonamide,

2-methyl-N-[2-(trifluoromethyl)benzyl]-1,3-benzothiazole-5-sulfonamide,

N-(4-bromo-3-fluorophenyl)-2-methyl-1,3-benzothiazole-5-sulfonamide,

2-methyl-N-[4-(trifluoromethyl)benzyl]-1,3-benzothiazole-5-sulfonamide,

N-[2-(4-tert-butylphenyl)ethyl]-2-methyl-1,3-benzothiazole-5-sulfonamide,

N-[2-(1H-indol-3-yl)ethyl]-2-methyl-1,3-benzothiazole-5-sulfonamide,

N-(4-iodobenzyl)-2-methyl-1,3-benzothiazole-5-sulfonamide,

N,N-diethyl-4-(2-{[(2-methyl-1,3-benzothiazol-5-yl)sulfonyl]amino}ethyl)benzamide,

2-methyl-N-[4-(trifluoromethoxy)benzyl]-1,3-benzothiazole-5-sulfonamide,

2-methyl-N-[(3-phenylisoxazol-5-yl)methyl]-1,3-benzothiazole-5-sulfonamide, and 2-methyl-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-1,3-benzothiazole-5-sulfonamide, or salts, solvates or solvated salts thereof.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

For the avoidance of doubt it is to be understood that in this specification 'C_{1-6}' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be, but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl, i-hexyl or t-hexyl. The term C_{1-3} alkyl having 1 to 3 carbon atoms and may be methyl, ethyl, n-propyl or i-propyl.

The term 'C_0' means "a bond" or "does not exist". For example when R^3 is C_0alkyl, R^3 is a bond and "arylC_0alkyl" is equivalent with "aryl", "C_2alkylOC_0alkyl" is equivalent with "C_2alkylO".

In this specification, unless stated otherwise, the term "alkenyl" includes both straight and branched chain alkenyl groups. The term "C_{2-6}alkenyl" having 2 to 6 carbon atoms and one or two double bonds, may be, but is not limited to vinyl, allyl, propenyl, butenyl, crotyl, pentenyl, or hexenyl, and a butenyl group may for example be buten-2-yl, buten-3-yl or buten-4-yl.

In this specification, unless stated otherwise, the term "alkynyl" includes both straight and branched chain alkynyl groups. The term "C_{2-6}alkynyl" having 2 to 6 carbon atoms and

one or two trippel bonds, may be, but is not limited to etynyl, propargyl, pentynyl or hexynyl and a butynyl group may for example be butyn-3-yl or butyn-4-yl.

In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring system. The term "C_{3-7}cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "heterocycloalkyl" denotes a 3- to 7-membered, non-aromatic, partially or completely saturated hydrocarbon group, which contains one ring and at least one heteroatom. Examples of said heterocycle include, but are not limited to pyrrolidinyl, pyrrolidonyl, piperidinyl, piperazinyl, morpholinyl, oxazolyl, 2-oxazolidonyl or tetrahydrofuranyl.

In this specification, unless stated otherwise, the term "aryl" refers to an optionally substituted monocyclic or bicyclic hydrocarbon unsaturated aromatic ring system. Examples of "aryl" may be, but are not limited to phenyl and naphthyl.

In this specification, unless stated otherwise, the term "heteroaryl" refers to an optionally substituted monocyclic or bicyclic ring system whereby at least one ring is aromatic independently from N, O or S. Examples of "heteroaryl" may be, but are not limited to pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, benzofuryl, indolyl, isoindolyl, benzimidazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl, triazolyl or oxazolyl.

In this specification, unless stated otherwise, the terms "heteroarylalkyl" and "phenylalkyl" refer to a substituent that is attached via the alkyl group to an aryl or heteroaryl group.

In this specification, unless stated otherwise, the terms "halo" and "halogen" may be fluoro, iodo, chloro or bromo.

In this specification, unless stated otherwise, the term "haloalkyl" means an alkyl group as defined above, which is substituted with halo as defined above. The term "C_{1-6}haloalkyl" may include, but is not limited to fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl or bromopropyl. The term "C_{1-6}haloalkylO" may include, but is not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy or difluoroethoxy.

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures.

The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts, solvates or solvated salts thereof. Salts for use in pharmaceutical formulations will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I.

A suitable pharmaceutically acceptable salt of the compounds of the invention is, for example, an acid-addition salt, for example a salt with an inorganic or organic acid. In addition, a suitable pharmaceutically acceptable salt of the compounds of the invention is an alkali metal salt, an alkaline earth metal salt or a salt with an organic base.

Other pharmaceutically acceptable salts and methods of preparing these salts may be found in, for example, Remington's Pharmaceutical Sciences (18^{th} Edition, Mack Publishing Co.).

Some compounds of formula I may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomeric and geometric isomers.

The invention also relates to any and all tautomeric forms of the compounds of formula I.

Medical use

Surprisingly, it has been found that the compounds according to the present invention are useful in therapy. The compounds of formula I, or salts, solvates or solvated salts thereof, as well as their corresponding active metabolites, exhibit a high degree of potency and selectivity for individual vanilloid receptor 1 (VR1) groups. Accordingly, the compounds of the present invention are expected to be useful in the treatment of conditions associated with excitatory activation of vanilloid receptor 1 (VR1).

The compounds may be used to produce an inhibitory effect of VR1 in mammals, including man.

VR1 are highly expressed the peripheral nervous system and in other tissues. Thus, it is expected that the compounds of the invention are well suited for the treatment of VR1 mediated disorders.

The compounds of formula I are expected to be suitable for the treatment of acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain. Examples of such disorder may be selected from the group comprising arthritis, rheumatoid arthritis, spondylitis and gout, fibromyalgia, low back pain and sciatica, post-operative pain, cancer pain, migraine and tension headache, visceral pains like chronic pelvic pain, cystitis, including interstitial cystitis, pancreatitis, renal and biliary colic, menstruation associated pain, pain related to ischeamic and angina, neuropathic pain disorders such as diabetic neuropathy, HIV neuropathy, chemotherapy induced neuropathies, post-herpetic neuralgia, post traumatic neuralgia and complex regional syndrome as well as itch.

Further relevant disorders may be selected from the group comprising gastro-esophageal reflux disease (GERD), functional gastrointestinal disorders (FGD) such as irritable bowel syndrome (IBS), irritable bowel syndrome (IBS), and functional dyspepsia (FD).

Further examples of disorders are overactive bladder ("OAB"), a term for a syndrome that encompasses urge incontinence, urgency and frequency. Compounds of the invention may alleviate urinary incontinence ("UI") the involuntary loss of urine that results from an inability of the bladder to retain urine as a consequence of either urge (urge incontinence), or physical or mental stress (stress incontinence).
Other relevant disorders may be psoriasis, and emesis.

Yet further relevant disorders are related to respiratory diseases and may be selected from the group comprising cough, asthma, chronic obstructive lung disease and emphysema, lung fibrosis and interstitial lung disease.
The VR1 inhibitor(s) for respiratory use, may be administrated by either an oral or inhaled route. The respiratory disease may be an acute and chronic illness and may be related to infection(s) and/or exposure to environmental pollution and/or irritants.
The compounds of formula I may also be used as antitoxin to treat (over-) exposure to VR1 activators like capsaicin, tear gas, acids or heat. Regarding heat, there is a potential use for VR1 antagonists in (sun-)burn induced pain, or inflammatory pain resulting from burn injuries.
The compounds may further be used for treatment of tolerance to VR1 activators.

One embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, in therapy.

Another embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of VR1 mediated disorders.

A further embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of acute and chronic pain.

Yet another embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of acute and chronic neuropathic pain.

Yet a further embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of acute and chronic inflammatory pain.

One embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of arthritis, rheumatoid arthritis, spondylitis and gout, fibromyalgia, low back pain and sciatica, post-operative pain, cancer pain, migraine and tension headache, visceral pains like chronic pelvic pain, cystitis, including interstitial cystitis, pancreatitis, renal and biliary colic, menstruation associated pain, pain related to ischeamic and angina, neuropathic pain disorders such as diabetic neuropathy, HIV neuropathy, chemotherapy induced neuropathies, post-herpetic neuralgia, post traumatic neuralgia and complex regional syndrome as well as itch.

Another embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of gastro-esophageal reflux disease, functional gastrointestinal disorders, irritable bowel syndrome, irritable bowel syndrome and functional dyspepsia.

A further embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of overactive bladder.

Yet a further embodiment of the invention relates to the use of the compound of formula I as hereinbefore defined, for the treatment of respiratory diseases selected from the group comprising of cough, asthma, chronic obstructive lung disease and emphysema, lung fibrosis and interstitial lung disease.

One embodiment of the invention relates to the use of the compound of formula I as hereinbefore defined, in the manufacture of a medicament for treatment of VR1 mediated disorders and for treatment of acute and chronic pain, acute and chronic neuropathic pain

and acute and chronic inflammatory pain, and respiratory diseases, and any other disorder mentioned above.

Another embodiment of the invention relates to a method of treatment of VR1 mediated disorders and acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain, and respiratory diseases, and any other disorder mentioned above, comprising administrering to a mammal, including man in need of such treatment, a therapeutically effective amount of the compounds of formula I, as hereinbefore defined.

A further embodiment of the invention relates to a pharmaceutical composition comprising a compound of formula I as hereinbefore defined, for use in treatment of VR1 mediated disorders and for treatment of acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain, and respiratory diseases, and any other disorder mentioned above.

In the context of the present specification, the term "therapy" and "treatment" includes prevention and prophylaxis, unless there are specific indications to the contrary. The terms "treat","therapeutic" and "therapeutically" should be construed accordingly.

In this specification, unless stated otherwise, the term "inhibitor" and "antagonist" mean a compound that by any means, partly or completely, blocks the transduction pathway leading to the production of a response by the ligand.

The term "disorder", unless stated otherwise, means any condition and disease associated with vanilloid receptor activity.

Non- Medical use

In addition to their use in therapeutic medicine, the compounds of the invention, or salts, solvates or solvated salts thereof, are also useful as pharmacological tools in the

development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of VR1 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

Pharmaceutical composition

According to one embodiment of the present invention there is provided a pharmaceutical composition comprising as active ingredient a therapeutically effective amount of the compound of formula I, or salts, solvates or solvated salts thereof, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

The composition may be in a form suitable for oral administration, for example as a tablet, pill, syrup, powder, granule or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration e.g. as an ointment, patch or cream or for rectal administration e.g. as a suppository.

In general the above compositions may be prepared in a conventional manner using one or more conventional excipients, pharmaceutical acceptable diluents and/or inert carriers.

Suitable daily doses of the compounds of formula I in the treatment of a mammal, including man, are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration.

The typical daily dose of the active ingredient varies within a wide range and will depend on various factors such as the relevant indication, severity of the illness being treated, the route of administration, the age, weight and sex of the patient and the particular compound being used, and may be determined by a physician.

Examples of pharmaceutical composition

The following illustrate representative pharmaceutical dosage forms containing a compound of formula I, or salts, solvates or solvated salts thereof, (hereafter compound X) for preventive or therapeutic use in mammals:

(a): Tablet	**mg/tablet**
Compound X	100
Lactose	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Capsule	**mg/capsule**
Compound X	10
Lactose	488.5
Magnesium stearate	1.5

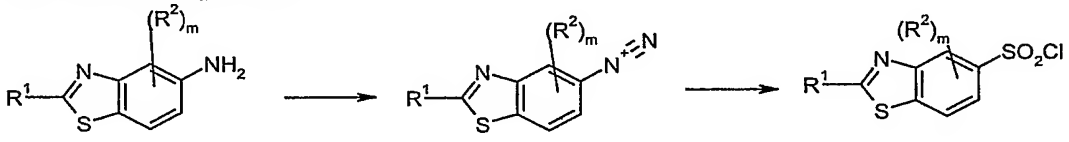
(c): Injection	**(50 mg/ml)**
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	(to adjust pH to 7.6)
Polyethylene glycol 400	4.5% w/v
Water for injection	up to 100%

The above compositions may be obtained by conventional procedures well known in the pharmaceutical art.

Methods of Preparation

General methods of preparation

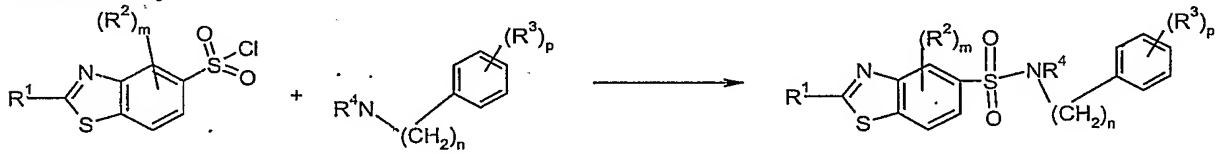
One embodiment of the invention relates to a process for the preparation of the compound of formula I, wherein R^1 to R^4, m, n and p, unless otherwise specified, are defined as in formula I, comprising;



II III IV

a) reaction of an aromatic amine of formula (II) with sodium nitrite in the presence of an acid such as hydrochloric acid, trifluoroacetic acid or acetic acid, to form a diazonium intermediate (III) which in turn may be reacted in-situ with sulphur dioxide or sodium sulfite in the presence of copper chloride to form an aromatic sulfonyl chloride (IV). This reaction may be performed in any manner known to the skilled person in the art. Suitable solvents to be used for this reaction may be water, acetone mixed with acids such as hydrochloric acid, sulphuric acid, acetic acid and TFA, or mixtures of the above. The temperature may be between 0 and 10°C and the reaction time may be between 0.5 and 30 h.

Followed by

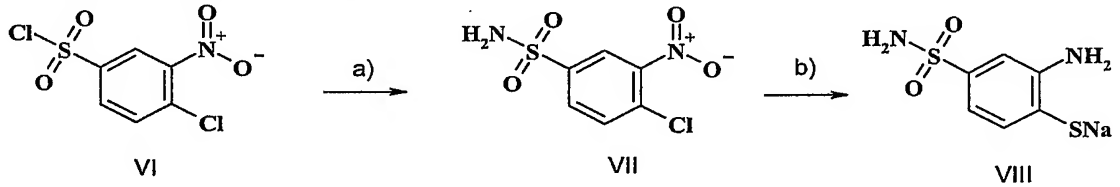


IV V I

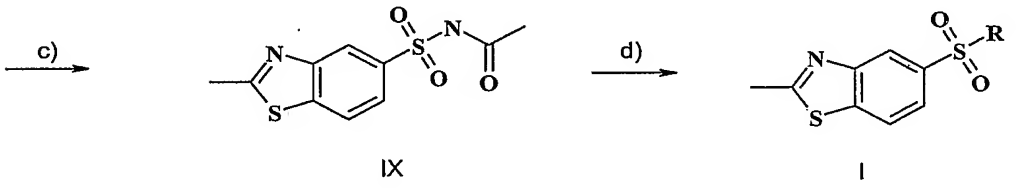
b) Reaction of an aromatic sulfonyl chloride (IV) with a properly substituted amine (V) in the presence of a base in a mixture of for example water and acetone.
Suitable solvents to be used for this reaction may be tertiary amides such as dimethylformamide and dimethylacetamide, halogenated hydrocarbons such as chloroform, dichloromethane and dichloroethane or aromatic and heteroaromatic compounds such as benzene, toluene, xylene, pyridine and lutidine or ethers such as ethyl ether, tetrahydrofuran and dioxane, or any mixtures thereof.
Catalysts such as heteroaromatic bases like pyridine and lutidine or tertiary amines like triethylamine, *N*-methylmorpholine and ethyl diisopropylamine may be used as well.

The temperature may be between 10 and 60°C and the reaction time may be between 3 and 30 h.

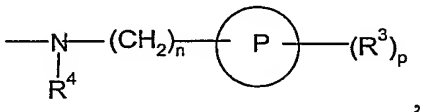
Another embodiment of the invention relates to a process for the preparation of the compound of formula I, wherein R^1 to R^4, m, n and p, unless otherwise specified, are defined as in formula I, comprising;



VI VII VIII



IX I

and wherein R is  ,

c) reaction of the sulfonylchloride VI with ammonia may be performed in suitable solvents like ethers or water, or any mixtures thereof, where ethers may be diethyl ether, dioxane, tetrahydrofurane and dimethylethylene glycol ether. Reaction of intermediate VII with sodium sulfide provides sulfide VIII, suitable solvents for this reaction may be water, acetonitrile, carbondisulfide, dimethylsulfoxide, or a mixture of thereof. Reaction of intermediate VIII to provide intermediate IX may be performed with acetic anhydride, acetic acid, or mixtures thereof, at about 100 °C followed by refluxing in acetic acid. Reaction of intermediate IX to provide the final compound I may be carried out in a two steps one pot sequence in which suitable solvents used in the first step may be $POCl_3$, dioxane, toluene. Suitable solvents to be used for the second step may be tertiary amides such as dimethylformamide and dimethylacetamide, halogenated hydrocarbons such as chloroform, dichloromethane and dichloroethane or aromatic and heteroaromatic

compounds such as benzene, toluene, xylene, pyridine and lutidine or ethers such as ethyl ether, tetrahydrofuran and dioxane, or any mixtures thereof.

Catalist agent such as heteroaromatic bases like pyridine and lutidine or tertiary amines like triethylamine, *N*-methylmorpholine and ethyl diisopropylamine may be used as well.

The temperature may be between 10 and 60°C and the reaction time may be between 3 and 30 h.

Examples of specific conditions for the different process steps are

a) NH3, 1,4-Dioxane, rt b) Na2S.9H2O, H2O, 100°C c) 1) Ac2O and AcOH, 100°C 2) AcOH, reflux, d) 1) POCl3 reflux 2) CH2Cl2, DIPEA, Amine, rt.

The above-described processes may be performed in way known to the skilled person.

Intermediates

A further embodiment of the invention relates to compounds *N*-[(2-methyl-1,3-benzothiazol-5-yl)sulfonyl]acetamide and allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate,

which may be used as intermediates in the preparation of compounds suited for the treatment of VR1 mediated disorders, especially for use as intermediates for the preparation of compounds of formula I.

Examples

The invention will now be illustrated by the following Examples in which,

generally :

(i) operations were carried out at ambient or room temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;

(ii) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

column chromatography (by the flash procedure) was performed on Silicycle silica gel (grade 230-400 mesh, 60 Å, cat. Numb. R10030B) or obtained from Silicycle, Quebec, Canada or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Phenomenex, Luna C-18 100Å preparative reversed-phase column;

The ^{1}H NMR spectra were recorded on a Varian or Brucker at 400 or 600 MHz. The mass spectra were recorded utilising electrospray (LC-MS; LC:Waters 2790, column XTerra MS C_8 2.5 μm 2.1X30 mm, buffer gradient H_2O+0.1%TFA:CH_3CN+0.04%TFA, MS: micromass ZMD// ammonium acetate buffer) ionisation techniques;

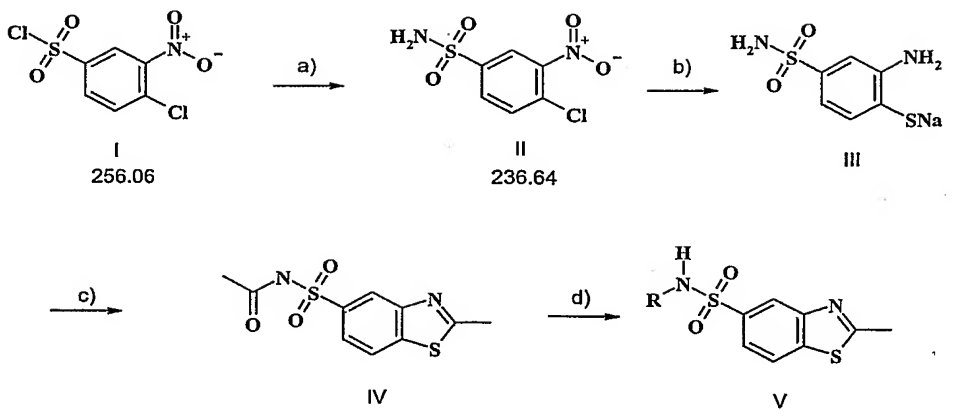
yields, where present, are not necessarily the maximum attainable;

(vi) intermediates were not necessarily fully purified but their structures and purity were assessed by thin layer chromatographic, HPLC and/or NMR analysis

(vii) the following abbreviations have been used:-

HPLC	high performance liquid chromatography
LC	liquid chromatography
MS	mass spectometry
ret. time	retention time
HCl	hydrochloric acid
TFA	trifluoroacetic acid
THF	tetrahydrofuran
DIPEA	N,N-diisopropylethylamine

General Procedure for the Preparation of acetyl sulphonamide intermediate IV used in examples 6 to 22.



a) NH_3, 1,4-Dioxane, RT b) $Na_2S{\cdot}9H_2O$, H_2O, 100 °C c) 1) Ac_2O and AcOH, 100 °C 2) AcOH, reflux d) 1) $POCl_3$ reflux 2) CH_2Cl_2, DIPEA, Amine, RT.

Intermediate 4-chloro-3-nitrobenzenesulfonamide II: To a solution of (7.5 g, 29.3 mmol) of 4-chloro-3-nitrobenzenesulfonyl chloride in dioxane 150 ml was bubbled NH_3 for one hour. The reaction was stirred until completion, then filtered, rinsed with dioxane and concentrated. The resulting solid was suspended in distilled water, filtered and dried. Yield 5.6 g, 23.7 mmol (80.7%). 1H NMR (400 MHz, DMSO-D6) δ ppm 7.75 (s, 2 H) 8.01 (d, *J*=8.40 Hz, 1 H) 8.07 (dd, *J*=8.40, 2.15 Hz, 1 H) 8.45 (d, *J*=2.15 Hz, 1 H).

Intermediate Sodium 2-amino-4-(aminosulfonyl)benzenethiolate III: To a suspension of 4-chloro-3-nitrobenzenesulfonamide (5.6 g, 23.7 mmol) in 100 ml of H_2O was added dropwise a solution of $Na_2S.9H_2O$ over 10 min. The yellow suspension was heated at reflux for 2 hours then concentrated and used as such without isolation in the next step.

Intermediate *N*-[(2-methyl-1,3-benzothiazol-5-yl)sulfonyl]acetamide IV: Sodium 2-amino-4-(aminosulfonyl)benzenethiolate III was dissolved in 200 ml of acetic anhydride and heated for 1 hour at 100 °C. To this was added 25 ml of acetic acid and the heating was continued for a further 1.5 hours. The reaction was then concentrated and taken into acetic acid and the reaction was heated at reflux until complete by LC-MS. The reaction was allowed to cool, filtered then rinsed with acetic acid followed by water. The resulting beige solid was dried under vacuum yielding 5.1g, 79 % of compound IV. 1H NMR (400 MHz,

DMSO-D6) δ ppm 1.91 (s, 3 H) 2.85 (s, 3 H) 7.87 (dd, *J*=8.50, 1.86 Hz, 1 H) 8.30 (dd, *J*=8.50, 0.49 Hz, 1 H) 8.35 (d, *J*=1.37 Hz, 1 H) 12.19 (s, 1 H).

Example 1

2-(hydroxymethyl)-*N*-[4-(trifluoromethyl)phenyl]-1,3-benzothiazole-5-sulfonamide.

Allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate (1.0 g, 3.78 mmol) is ground to a fine powder which is suspended in concentrated HCl (3.8 mL). The mixture is cooled to 5-10°C and a solution of sodium nitrite (0.332 g, 4.81 mmol) in water (0.63 mL) is added dropwise. The mixture is stirred at 5-10°C for 40 minutes and filtered under vacuum. While the diazotization reaction occurs sodium sulfite (1.192 g, 9.46 mmol) and copper sulfate (0.092 g, 0.575 mmol) are dissolved in concentrated HCl (8.8 mL) and water (2 mL). The mixture is cooled to 3-5°C and the filtrate (from the diazotization reaction) is added followed by a solution of sodium nitrite (1.192 g, 9.46 mmol) in water (2 mL). The reaction is stirred at 3-5°C for 1 hour and the precipitate is filtered, washed with water and dried under vacuum overnight. The sulfonyl chloride (0.727 g, 2.09 mmol) is dissolved in THF (6 mL). A saturated aqueous solution of sodium bicarbonate (1 mL) is added followed by 4-(trifluoromethyl)aniline (263 μL, 2.09 mmol). The reaction is stirred at room temperature for 1 hour. The aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated. The sulfonamide is dissolved in THF (25 mL) and 1M NaOH (25 mL) is added. The mixture is stirred at room temperature for 2 hours. Water is added and the aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with water and brine, dried with sodium sulfate, filtered and concentrated. The crude is purified by Gilson reverse phase HPLC eluting with acetonitrile and water containing 0.1% TFA to yield the end product (41 mg, 5%). 1H NMR (600 MHz, MeOD) δ ppm 5.04 (s, 2 H) 7.38 (d, *J*=8.45 Hz, 2 H) 7.59 (d, *J*=8.45 Hz, 2 H) 7.91 (d, *J*=8.45 Hz, 1 H) 8.23 (d, *J*=8.45 Hz, 1 H) 8.42 (s, 1 H); MS [MH+] calc. 389.0 found 388.8.

Example 2

***N*-biphenyl-4-yl-2-(hydroxymethyl)-1,3-benzothiazole-5-sulfonamide.**

Allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate (3.0 g, 11.35 mmol) is ground to a fine powder which is suspended in concentrated HCl (11.4 mL). The mixture is cooled to 5-10°C and a solution of sodium nitrite (0.995 g, 14.42 mmol) in water (1.9 mL) is added dropwise. The mixture is stirred at 5-10°C for 40 minutes and filtered under vacuum. While the diazotization reaction occurs sodium sulfite (3.577 g, 28.38 mmol) and copper sulfate (0.275 g, 1.73 mmol) are dissolved in concentrated HCl (26.4 mL) and water (6 mL). The mixture is cooled to 3-5°C and the filtrate (from the diazotization reaction) is added followed by a solution of sodium nitrite (3.577 g, 28.32 mmol) in water (6 mL). The reaction is stirred at 3-5°C for 1 hour and the precipitate is filtered, washed with water and dried under vacuum overnight. The sulfonyl chloride (0.400 g, 1.15 mmol) is dissolved in THF (4 mL). A saturated aqueous solution of sodium bicarbonate (1 mL) is added followed by 4-aminobiphenyl (0.195 g, 1.15 mmol). The reaction is stirred at room temperature for 1 hour. The aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated. The sulfonamide is dissolved in THF (14 mL) and 1M NaOH (14 mL) is added. The mixture is stirred at room temperature for 2 hours. Water is added and the aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with water and brine, dried with sodium sulfate, filtered and concentrated. The crude is purified by Gilson reverse phase HPLC eluting with acetonitrile and water containing 0.1% TFA to yield the end product (43 mg, 9%). 1H NMR (600 MHz, MeOD) δ ppm 4.93 (s, 2 H) 7.18 (d, *J*=8.70 Hz, 2 H) 7.27 (d, *J*=7.42 Hz, 1 H) 7.36 (t, *J*=7.68 Hz, 2 H) 7.46 (d, *J*=8.45 Hz, 2 H) 7.50 (d, *J*=7.68 Hz, 2 H) 7.79 (dd, *J*=8.45, 1.54 Hz, 1 H) 8.12 (d, *J*=8.71 Hz, 1 H) 8.28 (d, *J*=1.28 Hz, 1 H); MS [MH+] calc. 397.1 found 397.0.

Example 3

2-(hydroxymethyl)-*N*-[3-(trifluoromethyl)phenyl]-1,3-benzothiazole-5-sulfonamide.

Allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate (3.0 g, 11.35 mmol) is ground to a fine powder which is suspended in concentrated HCl (11.4 mL). The mixture is cooled to 5-10°C and a solution of sodium nitrite (0.995 g, 14.42 mmol) in water (1.9 mL) is added dropwise. The mixture is stirred at 5-10°C for 40 minutes and filtered under vacuum.

While the diazotization reaction occurs sodium sulfite (3.577 g, 28.38 mmol) and copper sulfate (0.275 g, 1.73 mmol) are dissolved in concentrated HCl (26.4 mL) and water (6 mL). The mixture is cooled to 3-5°C and the filtrate (from the diazotization reaction) is added followed by a solution of sodium nitrite (3.577 g, 28.32 mmol) in water (6 mL). The reaction is stirred at 3-5°C for 1 hour and the precipitate is filtered, washed with water and dried under vacuum overnight. The sulfonyl chloride (0.400 g, 1.15 mmol) is dissolved in THF (4 mL). A saturated aqueous solution of sodium bicarbonate (1 mL) is added followed by 3-(trifluoromethyl)aniline (143 μL , 1.15 mmol). The reaction is stirred at room temperature for 2 hours. The aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated. The sulfonamide is dissolved in THF (14 mL) and 1M NaOH. (14 mL) is added. The mixture is stirred at room temperature for 2 hours. Water is added and the aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with water and brine, dried with sodium sulfate, filtered and concentrated. The crude is purified by Gilson reverse phase HPLC eluting with acetonitrile and water containing 0.1% TFA to yield the end product (24mg, 5%). 1H NMR (600 MHz, MeOD) δ ppm 4.94 (s, 2 H) 7.30 - 7.35 (m, 2 H) 7.38 (d, *J*=7.94 Hz, 1 H) 7.40 (s, 1 H) 7.77 (dd, *J*=8.45, 1.54 Hz, 1 H) 8.13 (d, *J*=8.45 Hz, 1 H) 8.27 (d, *J*=1.28 Hz, 1 H); MS [MH+] calc. 389.0 found 388.8.

Example 4

2-(hydroxymethyl)-*N*-[4-(trifluoromethyl)benzyl]-1,3-benzothiazole-5-sulfonamide.

Allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate (3.0 g, 11.35 mmol) is ground to a fine powder which is suspended in concentrated HCl (11.4 mL). The mixture is cooled to 5-10°C and a solution of sodium nitrite (0.995 g, 14.42 mmol) in water (1.9 mL) is added dropwise. The mixture is stirred at 5-10°C for 40 minutes and filtered under vacuum. While the diazotization reaction occurs sodium sulfite (3.577 g, 28.38 mmol) and copper sulfate (0.275 g, 1.73 mmol) are dissolved in concentrated HCl (26.4 mL) and water (6 mL). The mixture is cooled to 3-5°C and the filtrate (from the diazotization reaction) is added followed by a solution of sodium nitrite (3.577 g, 28.32 mmol) in water (6 mL). The

reaction is stirred at 3-5°C for 1 hour and the precipitate is filtered, washed with water and dried under vacuum overnight. The sulfonyl chloride (0.400 g, 1.15 mmol) is dissolved in THF (4 mL). A saturated aqueous solution of sodium bicarbonate (1 mL) is added followed by 4-(trifluoromethyl)benzylamine (164 μL , 1.15 mmol). The reaction is stirred at room temperature for 2 hours. The aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated. The sulfonamide is dissolved in THF (14 mL) and 1M NaOH (14 mL) is added. The mixture is stirred at room temperature for 2 hours. Water is added and the aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with water and brine, dried with sodium sulfate, filtered and concentrated. The crude is purified by Gilson reverse phase HPLC eluting with acetonitrile and water containing 0.1% TFA to yield the end product (44 mg, 9%). 1H NMR (600 MHz, MeOD) δ ppm 4.20 (s, 2 H) 4.97 (s, 2 H) 7.36 (d, *J*=8.19 Hz, 2 H) 7.44 (d, *J*=7.94 Hz, 2 H) 7.80 (dd, *J*=8.45, 1.54 Hz, 1 H) 8.12 (d, *J*=8.19 Hz, 1 H) 8.23 (s, 1 H); MS [MH+] calc. 403.0 found 402.7.

Example 5

2-(hydroxymethyl)-*N*-[3-(trifluoromethyl)benzyl]-1,3-benzothiazole-5-sulfonamide.

Allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate (3.0 g, 11.35 mmol) is ground to a fine powder which is suspended in concentrated HCl (11.4 mL). The mixture is cooled to 5-10°C and a solution of sodium nitrite (0.995 g, 14.42 mmol) in water (1.9 mL) is added dropwise. The mixture is stirred at 5-10°C for 40 minutes and filtered under vacuum. While the diazotization reaction occurs sodium sulfite (3.577 g, 28.38 mmol) and copper sulfate (0.275 g, 1.73 mmol) are dissolved in concentrated HCl (26.4 mL) and water (6 mL). The mixture is cooled to 3-5°C and the filtrate (from the diazotization reaction) is added followed by a solution of sodium nitrite (3.577 g, 28.32 mmol) in water (6 mL). The reaction is stirred at 3-5°C for 1 hour and the precipitate is filtered, washed with water and dried under vacuum overnight. The sulfonyl chloride (0.400 g, 1.15 mmol) is dissolved in THF (4 mL). A saturated aqueous solution of sodium bicarbonate (1 mL) is added followed by 3-(trifluoromethyl)benzylamine (165 μL , 1.15 mmol). The reaction is stirred

at room temperature for 2 hours. The aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated. The sulfonamide is dissolved in THF (14 mL) and 1M NaOH (14 mL) is added. The mixture is stirred at room temperature for 2 hours. Water is added and the aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with water and brine, dried with sodium sulfate, filtered and concentrated. The crude is purified by Gilson reverse phase HPLC eluting with acetonitrile and water containing 0.1% TFA to yield the end product (8 mg; 2%). 1H NMR (600 MHz, MeOD) δ ppm 4.21 (s, 2 H) 4.97 (s, 2 H) 7.38 (d, *J*=7.68 Hz, 1 H) 7.42 (d, *J*=16.13 Hz, 2 H) 7.46 (d, *J*=7.42 Hz, 1 H) 7.79 (dd, *J*=8.45, 1.54 Hz, 1 H) 8.11 (d, *J*=8.45 Hz, 1 H) 8.27 (d, *J*=1.28 Hz, 1 H); MS [MH+] calc. 403.0 found 402.7.

Example 6

N-(4-isopropoxyphenyl)-2-methyl-1,3-benzothiazole-5-sulfonamide. 200 mg of *N*-[(2-methyl-1,3-benzothiazol-5-yl)sulfonyl]acetamide was heated in $POCl_3$ at 110 °C overnight until complete conversion to the chloride. The solution was concentrated to dryness and placed under high vacuum. The brown oil was taken into 4 ml of dry CH_2Cl_2. To this was added 1.5 equivalents of 4-isopropoxyaniline and 3 equivalents of DIPEA. After stirring the reaction overnight, it was then concentrated, and taken into ethyl acetate and 1 N HCl. The aqueous phase is separated and the organic layer washed with 2 N $NaHCO_3$, then brine and dried over Na_2SO_4, filtered and concentrated. Purification was then done by silica gel chromatography with either ethyl acetate/heptane. 1H NMR (600 MHz, $CDCl_3$) δ ppm 1.29 (d, J=6.14 Hz, 6 H) 2.86 (s, 3 H) 4.41 - 4.48 (m, 1 H) 6.31 (s, 1 H) 6.72 (d, J=8.70 Hz, 2 H) 6.95 (d, J=8.96 Hz, 2 H) 7.64 (dd, J=8.45, 1.79 Hz, 1 H) 7.86 (d, J=8.19 Hz, 1 H) 8.31 (d, J=1.79 Hz, 1 H). MS [MH+] calc. 363.1 found 363.0.

Example 7

N-(4-tert-butylphenyl)-2-methyl-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using 4-tert-butylaniline. 1H NMR (600 MHz, $CDCl_3$) δ ppm 1.24 (s, 9 H) 2.86 (s, 3 H) 6.74 (s, 1 H) 7.00 (d, J=8.19 Hz, 2 H) 7.23 (d, J=8.19 Hz, 2 H) 7.72

(d, J=8.45 Hz, 1 H) 7.87 (d, J=8.19 Hz, 1 H) 8.39 (s, 1 H). MS [MH+] calc. 361.1 found 361.0.

Example 8

2-methyl-N-[6-(trifluoromethyl)pyridin-3-yl]-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using 3-amino-6-trifluromethylpyridine. 1H NMR (600 MHz, $CDCl_3$) δ ppm 2.92 (s, 3 H) 7.63 (dd, J=8.32, 2.18 Hz, 1 H) 7.73 (d, J=8.45 Hz, 1 H) 7.96 (dd, J=8.45, 1.79 Hz, 1 H) 8.05 (d, J=8.45 Hz, 1 H) 8.36 (d, J=2.30 Hz, 1 H) 8.45 (d, J=1.79 Hz, 1 H). MS [MH+] calc. 374.0 found 373.7

Example 9

2-methyl-N-[3-(trifluoromethyl)phenyl]-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using 3-trifluromethylaniline. 1H NMR (600 MHz, $CDCl_3$) δ ppm 2.87 (s, 3 H) 6.77 (s, 1 H) 7.29 - 7.34 (m, 2 H) 7.35 - 7.39 (m, 2 H) 7.73 (dd, J=8.45, 1.79 Hz, 1 H) 7.90 (d, J=8.19 Hz, 1 H) 8.38 (d, J=1.79 Hz, 1 H). MS [MH+] calc. 373.0 found 372.8.

EXAMPLE 10

N-(4-bromophenyl)-2-methyl-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using 4-bromoaniline. 1H NMR (600 MHz, DMSO-D6) δ ppm 2.83 (s, 3 H) 7.06 (d, J=8.96 Hz, 2 H) 7.41 (d, J=8.96 Hz, 2 H) 7.72 (d, J=8.45 Hz, 1 H) 8.21 (s, 1 H) 8.24 (d, J=8.45 Hz, 1 H) 10.56 (s, 1 H). MS [MH+] calc. 383.0 found 382.7.

Example 11

2-methyl-N-[2-(4-methylphenyl)ethyl]-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using 2-(p-tolyl)ethylamine. 1H NMR (600 MHz, DMSO-D6) δ ppm 2.21 (s, 3 H) 2.60 (t, J=7.42 Hz, 2 H) 2.84 (s, 3 H) 2.90 - 2.98 (m, 2 H) 6.97 - 7.03 (m, 4 H) 7.74 (dd, J=8.45, 1.54 Hz, 1 H) 7.79 (t, J=5.76 Hz, 1 H) 8.20 (d, J=1.54 Hz, 1 H) 8.24 (d, J=8.45 Hz, 1 H) MS [MH+] calc. 347.1 found 347.0

Example 12

N-[2-(4-bromophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using 4-bromophenethylamine. 1H NMR (600 MHz, DMSO-D6) δ ppm 2.64 (t, J=7.17 Hz, 2 H) 2.84 (s, 3 H) 2.95 - 3.00 (m, 2 H) 7.09 (d, J=8.45 Hz, 2 H) 7.37 (d, J=8.45 Hz, 2 H) 7.72 (dd, J=8.45, 1.79 Hz, 1 H) 7.80 (t, J=5.63 Hz, 1 H) 8.19 (d, J=1.79 Hz, 1 H) 8.23 (d, J=8.45 Hz, 1 H). MS [MH+] calc. 410.9 found 410.7.

Example 13

2-methyl-N-[2-(trifluoromethyl)benzyl]-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using 2-trifluoromethylbenzylamine. 1H NMR (400 MHz, DMSO-D6) δ ppm 2.85 (s, 3 H) 4.16 (d, J=6.05 Hz, 2 H) 7.42 (t, J=7.42 Hz, 1 H) 7.55 - 7.66 (m, 3 H) 7.77 (dd, J=8.40, 1.95 Hz, 1 H) 8.24 (d, J=1.76 Hz, 1 H) 8.26 (dd, J=8.40, 0.59 Hz, 1 H) 8.44 (t, J=6.15 Hz, 1 H). MS [MH+] calc. 387.0 found 386.7.

Example 14

N-(4-bromo-3-fluorophenyl)-2-methyl-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using 4-bromo-3-fluoroaniline. 1H NMR (600 MHz, DMSO-D6) δ ppm 2.82 (s, 3 H) 6.90 (dd, J=8.70, 2.30 Hz, 1 H) 7.07 (dd, J=10.50, 2.30 Hz, 1 H) 7.54 (t, J=8.32 Hz, 1 H) 7.75 (dd, J=8.58, 1.66 Hz, 1 H) 8.25 (s, 1 H) 8.26 (d, J=5.89 Hz, 1 H) 10.85 (s, 1 H). MS [MH+] calc. 400.9 found 400.8.

Example 15

2-methyl-N-[4-(trifluoromethyl)benzyl]-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using 4-trifluoromethylbenzylamine. 1H NMR (600 MHz, DMSO-D6) δ ppm 2.84 (s, 3 H) 4.10 - 4.17 (m, 2 H) 7.43 (d, J=8.19 Hz, 1 H) 7.56 (d, J=8.19 Hz, 2 H) 7.76 (d, J=8.19 Hz, 2 H) 8.17 (s, 1 H) 8.23 (d, J=8.45 Hz, 1 H) 8.43 (t, J=6.53 Hz, 1 H). MS [MH+] calc. 387.0 found 386.8.

Example 16

N-[2-(4-tert-butylphenyl)ethyl]-2-methyl-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using 2-(4-tert-butylphenyl)ethylamine. 1H NMR (400 MHz, DMSO-D6) δ ppm 1.22 (s, 9 H) 2.55 - 2.67 (m, 2 H) 2.84 (s, 3 H) 2.88 - 3.00 (m, 2 H) 7.02 - 7.07 (m, 2 H) 7.21 - 7.26 (m, 2 H) 7.76 (dd, J=8.40, 1.76 Hz, 1 H) 7.80 (t, J=5.86 Hz, 1 H) 8.22 - 8.27 (m, 2 H). MS [MH+] calc. 389.1 found 389.0.

Example 17

N-[2-(1H-indol-3-yl)ethyl]-2-methyl-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using tryptamine. 1H NMR (400 MHz, DMSO-D6) δ ppm 2.76 (t, *J*=7.62 Hz, 2 H) 2.82 - 2.86 (m, 3 H) 2.97 - 3.05 (m, 2 H) 6.90 (t, 1 H) 6.98 - 7.04 (m, 1 H) 7.09 (d, *J*=2.15 Hz, 1 H) 7.30 (dd, *J*=16.01, 7.81 Hz, 2 H) 7.77 (dd, *J*=8.30, 1.86 Hz, 1 H) 7.86 (t, *J*=5.76 Hz, 1 H) 8.21 - 8.27 (m, 2 H) 10.79 (s, 1 H). MS [MH+] calc. 372.1 found 372.0.

Example 18

N-(4-iodobenzyl)-2-methyl-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using 4-iodobenzylamine. 1H NMR (400 MHz, DMSO-D6) δ ppm 2.85 (s, 3 H) 3.96 (d, *J*=6.45 Hz, 2 H) 6.99 (d, *J*=8.59 Hz, 2 H) 7.53 (d, *J*=8.40 Hz, 2 H) 7.73 (dd, *J*=8.40, 1.95 Hz, 1 H) 8.14 (d, *J*=1.37 Hz, 1 H) 8.22 (dd, *J*=8.40, 0.59 Hz, 1 H) 8.29 (t, *J*=6.35 Hz, 1 H). MS [MH+] calc. 444.9 found 444.7.

Example 19

N,N-diethyl-4-(2-{[(2-methyl-1,3-benzothiazol-5-yl)sulfonyl]amino}ethyl)benzamide. The procedure of example 6 was followed using 4-(2-amino-ethyl)-N,N-diethyl-benzamide. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.98 - 1.14 (m, 6 H) 2.70 (t, *J*=7.32 Hz, 2 H) 2.84 (s, 3 H) 2.95 - 3.03 (m, 2 H) 3.15 (s, 2 H) 3.39 (s, 2 H) 7.15 - 7.23 (m, 4 H) 7.73 - 7.77 (m, 1 H) 7.84 (t, *J*=5.76 Hz, 1 H) 8.24 (s, 1 H) 8.25 (d, *J*=6.64 Hz, 1 H). MS [MH+] calc. 432.1 found 432.0.

Example 20

2-methyl-N-[4-(trifluoromethoxy)benzyl]-1,3-benzothiazole-5-sulfonamide: The procedure of example 6 was followed using 4-trifluoromethoxybenzylamine. 1H NMR (400 MHz, DMSO-D6) δ ppm 2.84 (s, 3 H) 4.04 (d, *J*=6.25 Hz, 2 H) 7.20 (d, *J*=8.20 Hz, 2 H) 7.33 (d, *J*=8.79 Hz, 2 H) 7.74 (dd, *J*=8.40, 1.76 Hz, 1 H) 8.20 (d, *J*=1.76 Hz, 1 H) 8.22 (d, *J*=8.40 Hz, 1 H) 8.34 (t, *J*=6.45 Hz, 1 H). MS [MH+] calc. 403.0 found 402.7.

Example 21

2-methyl-N-[(3-phenylisoxazol-5-yl)methyl]-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using (3-phenyl-5-isoxazolyl)methanamine. 1H NMR (400 MHz, DMSO-D6) δ ppm 2.78 (s, 3 H) 4.28 (d, *J*=6.05 Hz, 2 H) 6.62 (s, 1 H) 7.41 - 7.48 (m, 3 H) 7.57 - 7.62 (m, 2 H) 7.75 (dd, *J*=8.40, 1.76 Hz, 1 H) 8.20 (d, *J*=8.40 Hz, 1 H) 8.22 (d, *J*=1.56 Hz, 1 H) 8.60 (t, *J*=6.25 Hz, 1 H). MS [MH+] calc. 386.1 found 385.8

Example 22

2-methyl-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-1,3-benzothiazole-5-sulfonamide. The procedure of example 6 was followed using (2-phenyl-1,3-thiazol-4-yl)methylamine. 1H NMR (400 MHz, DMSO-D6) δ ppm 2.78 (s, 3 H) 4.19 (d, *J*=6.05 Hz, 2 H) 7.37 - 7.45 (m, 4 H) 7.63 - 7.72 (m, 3 H) 8.11 (d, *J*=8.40 Hz, 1 H) 8.20 (d, *J*=1.56 Hz, 1 H) 8.38 (t, *J*=6.15 Hz, 1 H). MS [MH+] calc. 402.0 found 401.7.

Pharmacology

1. hVR1 FLIPR (Fluorometric Image Plate Reader) screening assay

Transfected CHO cells, stably expessing hVR1 (15,000 cells/well) are seeded in 50 ul media in a black clear bottom 384 plate (Greiner) and grown in a humidified incubator (37°C, 2% CO_2), 24-30 hours prior to experiment.

Subsequently, the media is removed from the cell plate by inversion and 2 μM Fluo-4 is added using a multidrop (Labsystems). Following the 40 minutes dye incubation in the

dark at 37°C and 2% CO_2, the extracellular dye present is washed away using an EMBLA (Scatron), leaving the cells in 40ul of assay buffer (1 X HBSS, 10 mM D-Glucose, 1 mM $CaCl_2$, 10 mM HEPES, 10 X 7.5% $NaHCO_3$ and 2.5 mM Probenecid).

FLIPR assay - IC_{50} determination protocol

For IC_{50} determinations the fluorescence is read using FLIPR filter 1 (em 520-545 nM). A cellular baseline recording is taken for 30 seconds, followed by a 20 µl addition of 10, titrated half-log concentrations of the test compound, yielding cellular concentration ranging from 3 µM to 0.1 nM. Data is collected every 2 seconds for a further 5 minutes prior to the addition of a VR1 agonist solution: either 50 nM solution of capsaicin or MES (2-[N-morpholino] ethanesulfonic acid) buffer (pH 5.2), by the FLIPR pipettor. The FLIPR continues to collect data for a further 4 minutes. Compounds having antagonistic properties against the hVR1 will inhibit the increase in intracellular calcium in response to the capsaicin addition. This consequently leading to a reduction in fluorescence signal and providing a reduced fluorescence reading, compared with no compound, buffer controls. Data is exported by the FLIPR program as a sum of fluorescence calculated under the curve upon the addition of capsaicin. Maximum inhibition, Hill slope and IC_{50} data for each compound are generated.

List of abbreviations

VR1	vanilloid receptor 1
IBS	irritable bowel syndrome
IBD	inflammatory bowel disease
GERD	gastro-esophageal reflux disease
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
EGTA	Ethylene glycol-bis(2-aminoethylether)-*N,N,N',N'*-tetraacetic acid
EMBLA	Skatron, Plate Cell Washer, from Molecular Devices company
HBSS	Hank's Balanced Salt Solution
MES	(2-[N-Morphholino]ethanesulfonic acid) Hydrate, Sigma cat# M-5287
NUT	Nutrient mixture F-12, medium for culturing cells

MEM Minimal Eagle Medium

Results

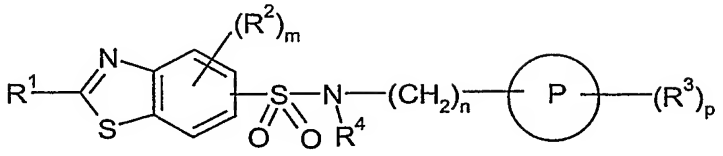
Typical IC_{50} values as measured in the assays described above are 10 μM or less. In one aspect of the invention the IC_{50} is below 10 μM.

Table 1. Specimen results from the hVR1 FLIPR .

Compound No.	**IC_{50} nM (agonist)**
5	2870

CLAIMS

1. A compound of formula I



(I)

wherein:

ring P is C_{6-10}aryl, C_{3-11}cycloalkyl or C_{5-10}heteroaryl;

R^1 is H, C_{1-4}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, $COOC_{0-6}$alkyl, NH_2, NHC_{1-6}alkyl, $N(C_{1-6}alkyl)_2$, NH(aryl) or $N(aryl)_2$;

R^2 is H, C_{1-4}alkyl, halo, hydroxyC_{0-6}alkyl or C_{1-6}alkylOC_{0-6}alkyl;

m is 0, 1, 2 or 3;

n is 0, 1, 2, 3, 4 or 5;

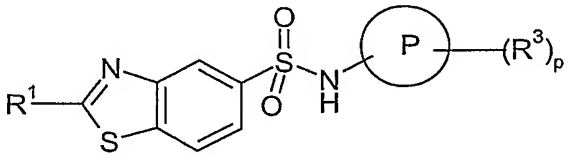
R^3 is NO_2, NH_2C_{0-6}alkyl, halo, $N(C_{1-6}alkyl)_2C_{0-6}$alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{5-6}arylC_{0-6}alkyl, C_{5-6}heteroarylC_{0-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{3-7}heterocycloalkylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, C_{1-6}alkylSC_{0-6}alkyl, C_{1-6}alkylNC_{0-6}alkyl, $(C_{0-6}alkyl)_2NC(O)C_{0-6}$alkyl, $(C_{0-6}alkyl)_2OC(O)C_{0-6}$alkyl or $(C_{0-6}alkyl)_2C(O)OC_{0-6}$alkyl;

p is 1, 2, 3, 4 or 5; and

R^4 is H, C_{1-6}alkyl, arylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl or $N(C_{1-6}alkyl)_2C_{0-6}$alkyl,

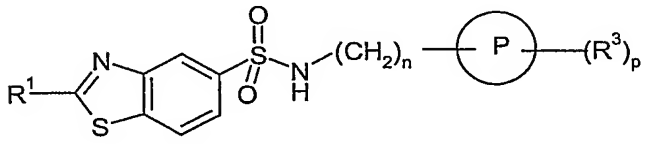
or salts, solvates or solvated salts thereof.

2. A compound of formula Ib wherein wherein R^1, R^3, m, p and P are as defined as in claim 1, and n is 0 and R^2 and R^4 are H.



(Ib)

3. A compound of formula Ic, wherein R^1, R^3, p, m and P are as defined as in claim 1, and n is 1, 2, 3, 4 or 5 and R^2 and R^4 are H.



(Ic)

4. The compound according to any one of claims 1 or 3 wherein ring P is phenyl.

5. The compound according to any one of claims 1 or 3 wherein R^1 is methyl or hydroxyC_{1-3}alkyl.

6. The compound according to any one of claims 1 to 3 wherein R^3 is phenyl, fluoromethyl, difluoromethyl or trifluoromethyl.

7. The compounds selected from the group consisting of
2-(hydroxymethyl)-*N*-[4-(trifluoromethyl)phenyl]-1,3-benzothiazole-5-sulfonamide,
N-biphenyl-4-yl-2-(hydroxymethyl)-1,3-benzothiazole-5-sulfonamide,
2-(hydroxymethyl)-*N*-[3-(trifluoromethyl)phenyl]-1,3-benzothiazole-5-sulfonamide,
2-(hydroxymethyl)-*N*-[4-(trifluoromethyl)benzyl]-1,3-benzothiazole-5-sulfonamide,
2-(hydroxymethyl)-*N*-[3-(trifluoromethyl)benzyl]-1,3-benzothiazole-5-sulfonamide,
N-(4-isopropoxyphenyl)-2-methyl-1,3-benzothiazole-5-sulfonamide,
N-(4-tert-butylphenyl)-2-methyl-1,3-benzothiazole-5-sulfonamide,
2-methyl-N-[6-(trifluoromethyl)pyridin-3-yl]-1,3-benzothiazole-5-sulfonamide,
2-methyl-N-[3-(trifluoromethyl)phenyl]-1,3-benzothiazole-5-sulfonamide,
N-(4-bromophenyl)-2-methyl-1,3-benzothiazole-5-sulfonamide,
2-methyl-N-[2-(4-methylphenyl)ethyl]-1,3-benzothiazole-5-sulfonamide,
N-[2-(4-bromophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-sulfonamide,

2-methyl-N-[2-(trifluoromethyl)benzyl]-1,3-benzothiazole-5-sulfonamide,
N-(4-bromo-3-fluorophenyl)-2-methyl-1,3-benzothiazole-5-sulfonamide,
2-methyl-N-[4-(trifluoromethyl)benzyl]-1,3-benzothiazole-5-sulfonamide,
N-[2-(4-tert-butylphenyl)ethyl]-2-methyl-1,3-benzothiazole-5-sulfonamide,
N-[2-(1H-indol-3-yl)ethyl]-2-methyl-1,3-benzothiazole-5-sulfonamide,
N-(4-iodobenzyl)-2-methyl-1,3-benzothiazole-5-sulfonamide,
N,N-diethyl-4-(2-{[(2-methyl-1,3-benzothiazol-5-yl)sulfonyl]amino}ethyl)benzamide,
2-methyl-N-[4-(trifluoromethoxy)benzyl]-1,3-benzothiazole-5-sulfonamide,
2-methyl-N-[(3-phenylisoxazol-5-yl)methyl]-1,3-benzothiazole-5-sulfonamide, and
2-methyl-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-1,3-benzothiazole-5-sulfonamide,
or salts, solvates or solvated salts thereof.

8. The compound according to any one of claims 1 to 7, for use in therapy.

9. Use of the compound according to any one of claims 1 to 7, in treatment of VR1 mediated disorders.

10. The use according to claim 9 for treatment of acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain.

11. The use according to claim 9 for treatment of respiratory diseases.

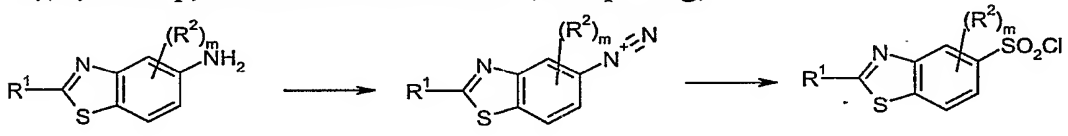
12. A method of treatment of VR1 mediated disorders and for treatment of acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain, and respiratory diseases, comprising administrering to a mammal, including man in need of such treatment, a therapeutically effective amount of the compound of formula I, according to any one of claims 1 to 7.

13. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of formula I, according to any one of claims 1 to 7, in

association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

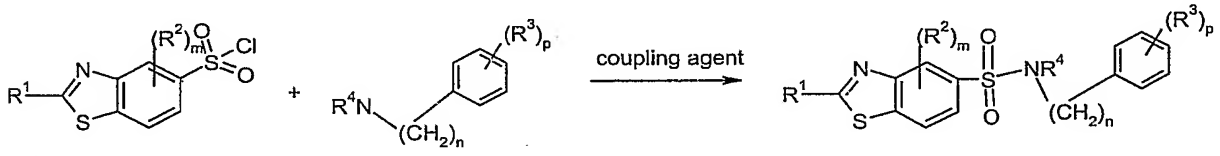
14. The pharmaceutical formulation according to claim 13, for use in the treatment of VR1 mediated disorders and for treatment of acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain, and respiratory diseases.

15. A processes for the preparation of the compound according to claim 1, wherein R^1 to R^4, m, n and p, are defined as in claim 1, comprising;



II III IV

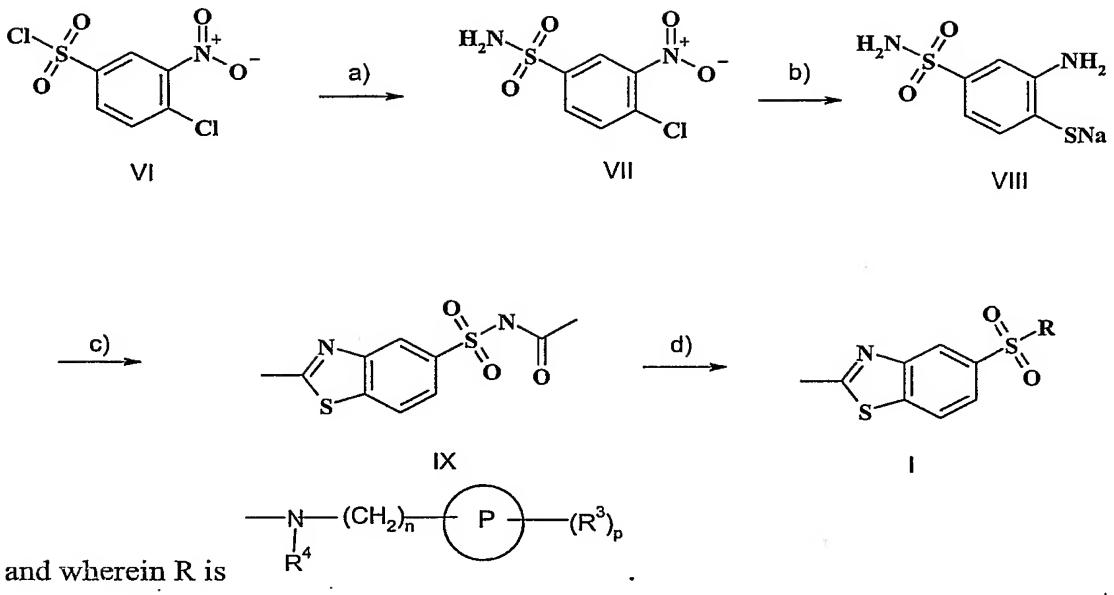
reaction of an aromatic amine of formula (II) with sodium nitrite in the presence of an acid to form a diazonium intermediate (III) which in turn is reacted in-situ with sulphur dioxide or sodium sulfite in the presence of copper chloride to form an aromatic sulfonyl chloride (IV), followed by



IV V I

b) reaction of an aromatic sulfonyl chloride (IV) with a properly substituted amine (V) in the presence of a base.

16. The process for the preparation of the compound of formula I, wherein R^1 to R^4, m, n and p, are defined as in claim 1, comprising;



and wherein R is

17. Compounds *N*-[(2-methyl-1,3-benzothiazol-5-yl)sulfonyl]acetamide and allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate.

18. Use the compounds according to claim 17 as intermediates in the preparation of the compound of formula I.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/001965

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9-12
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 9-12 relates to a method of treatment of the human or animal body by therapy /Rule 39.1(iv). Nevertheless, a search has been carried out for this claim, based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1: Claims 1-16 and part of claims 17-18.
2: Part of claims 17-18.

In order to fulfil the requirements of unity of invention, it is necessary that the intermediate compounds are closely

.../...

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-16, partly 17-18

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Box III

interconnected with the end products. Such close connection requires that the essential structural part of the end product is incorporated by the intermediate compound. However, the present application lacks a single general inventive concept based on the above principle. This leads to the presence of the subjects listed below, each falling under its own restricted inventive concept.

1: Claims 1-16 and the part of claims 17-18 relating to N-[(2methyl-1,3-benzotiazol-5-yl)sulfonyl]acetamide regarding novel compounds with formula (I), formulations and use thereof as well as the intermediate N-[(2methyl-1,3-benzotiazol-5-yl)sulfonyl]acetamide.

2: The part of claims 17-18 relating to allyl (5-amino-1,3-benzotiazol-2-yl)methyl carbonate regarding the intermediate allyl (5-amino-1,3-benzotiazol-2-yl)methyl carbonate.

A partial search was carried out, which related to the invention 1 above.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/001965

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File REGISTRY; SeeRN 670230-81-6, 670230-56-5, 670230-17-8, 634169-17-8,540512-24-1, 446052-22-8, 356098-50-5, 356084-71-4, 456084-67-8, 356084-64-5, 356077-97-9 --	1-2
X	WO 0177092 A1 (SAMSUNG ELECTRONICS CO., LTD.), 18 October 2001 (18.10.2001), see page 101, table 2, compoundsno 1,3 and 5 --	1-2

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 2006	15 -05- 2006
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/MP Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/001965

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1944:16158, Document no. 38:161158, Arnold, Herbert: "Thiocyanogenation of N-alkylanilines and sulfanilamides, & Arch. Pharm. (1941), 279, 181-6, RN 798551-35-6	1-2
X	STN International, file CAPLUS, CAPLUS accession no. 1970:66857, Document no. 72:66857, Couquelet, Jacques et al: "Preparation and properties of some 2-amino-6-sulfonamidobenzothiazoles", Bulletin de la Societe de Pharmacie de Marseille (1967), 16(63), 201-7, & RN 25742-24-9, RN 25742-25-0, RN 25745-08-8, RN 25745-09-9	1-2
X	STN International, file CAPLUS, CAPLUS accession no. 1997:351528, document no. 127:103691, Parvu, Dorel: "Conductometric determination of some 2-aminobenzothiazole-6-sulfonamides"; & Revista de Chimie (Bucharest) (1996), 57(11), 1009-1014, RN 25742-24-9, RN 192119-44-1	1-2
X	STN International, file CAPLUS, CAPLUS accession no. 1969:68231, document no. 70:68231, Libeer, Marcel J. et al: "Synthesis of x-sulfo-2-methylbenzothiazole isomers"; & Industrie Chimique Belge (1967), 32 (Spec. no.), 66-7, rn 21431-24-3	17
X	WO 2004096784 A1 (ASTRAZENECA AB), 11 November 2004 (11.11.2004)	1-18
X	WO 2004043369 A2 (SMITHKLINE BEECHAM CORPORATION), 27 May 2004 (27.05.2004), claim 1	1-16

International patent classification (IPC)

C07D 277/62 (2006.01)
A61K 31/381 (2006.01)
A61P 25/00 (2006.01)
C07D 277/64 (2006.01)
C07D 277/68 (2006.01)
C07D 277/82 (2006.01)

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Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

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